Amendments to the Specification (Attorney Docket No. 0272US310)

Please amend the Specification as follows:

1) The paragraph beginning at page 5, line 18 should be replaced with the following replacement paragraph:

With markings:

Fig. 1 shows the clotting time vs. concentration for [G237GAA]rhFVIIa when assayed in the "Whole Blood Assay". For comparison, the result fro rhFVIIa is included.

~~● rhFVIIa;~~

~~□ [G237GAA]rhFVIIa.~~

Without markings:

Fig. 1 shows the clotting time vs. concentration for [G237GAA]rhFVIIa when assayed in the "Whole Blood Assay". For comparison, the result fro rhFVIIa is included.

2) The paragraph beginning at page 23, line 5 should be replaced with the following replacement paragraph:

With markings:

It will be understood that any of the amino acid changes, in particular substitutions, specified in this section can be combined with any of the amino acid changes, in particular substitutions, specified in the other sections herein disclosing specific amino acid changes. For instance, any of the glycosylated polypeptides variants disclosed in the present section having introduced and/or removed at least one glycosylation site may further be conjugated to a polymer molecule, such as polyethylene glycol (PEG)~~PEG~~, or any other non-polypeptide moiety.

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3) The paragraph beginning at page 24, line 9 should be replaced with the following replacement paragraph:

With markings:

While the non-polypeptide moiety according to this aspect of the invention may be any molecule which when using the given conjugation method has cysteine as an attachment group, it is preferred that the non-polypeptide moiety is a polymer molecule. The polymer molecule may be any of the molecules mentioned in the section entitlted "Conjugation to a polymer molecule", but is preferably selected from the group consisting of linear or branched polyethylene glycol or another polyalkylene oxide. In a particular interesting embodiment the polymer molecule is PEG, such as vinyl sulfone polyethylene glycol (VS-PEG) ~~VS PEG~~.

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4) The paragraph beginning at page 2, line 18 should be replaced with the following replacement paragraph:

With markings:

Commercial preparations of recombinant human FVIIa (rhFVIIa) are sold under the tradename NOVOSEVEN® ~~NovoSeven®~~. NOVOSEVEN® ~~NovoSeven®~~ is indicated for the treatement of bleeding episodes in hemophilia A or B patients. NOVOSEVEN® ~~NovoSeven®~~ is the only rhFVIIa for effective and reliable treatment of bleeding episodes available on the market.

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5) The paragraph beginning at page 3, line 5 should be replaced with the following replacement paragraph:

With markings:

A circulating rhFVIIa half-life of 2.3 hours was reported in "Summary Basis for Approval for NOVOSEVEN® ~~NovoSeven®~~", FDA reference number 96-0597. Relatively high doses of frequent

administration are necessary to reach and sustain the desired therapeutic or phrophylactic effect. As a consequence, adequate dose regulation is difficult to obtain and the need for frequent intravenous administrations imposes restrictions on the patient's way of living.

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6) The paragraph beginning at page 4, line 21 should be replaced with the following replacement paragraph:

With markings:

The present invention provides improved recombinant FVII or FVIIa variants comprising at least one amino acid modification in a position selected from the group consisting of 196, 237 and 341. These amino acid modifications result in an altered binding of FVIIa to TFPI. As indicated above, the resulting molecules have one or more improved properties as compared to commercially available rhFVIIa, such as NOVOSEVEN® ~~NovoSeven®~~.

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7) The paragraph beginning at page 31, line 29 should be replaced with the following replacement paragraph:

With markings:

The polypeptide variant of the invention is administered to patients in a therapeutically effective dose, normally one approximately paralleling that employed in therapy with rhFVII such as NOVOSEVEN® ~~NovoSeven®~~, or at lower dosage. By "therapeutically effective dose" herein is meant a dose that is sufficient to produce the desired effects in relation to the condition for which it is administered. The exact dose will depend on the circumstances, and will be ascertainable by one skilled in the art using known techniques. Normally, the dose should be capable of preventing or lessening the

severity or spread of the condition or indication being treated. It will be apparent to those of skill in the art that an effective amount of a polypeptide variant or composition of the invention depends, *inter alia*, upon the disease, the dose, the administration schedule, whether the polypeptide variant or composition is administered alone or in conjunction with the other therapeutic agents, the plasma half-life of the compositions, and the general health of the patient.

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8) The paragraph beginning at page 36, line 25 should be replaced with the following replacement paragraph:

With markings:

ELISA Assay

FVII/FVIIa (or variant) concentrations are determined by ELISA. Wells of a microtiter plate are coated with an antibody directed against the protease domain using a solution of 2 µg/ml in PBS (100 µl per well). After overnight coating at R.T. (room temperature), the wells are washed 4 times with THT buffer (100 mM NaCL, 50 mM Tris-HCl pH 7.2 0.05% Tween-20). Subsequently, 200 µl of 1% Casein (diluted from 2.5% stock using 100 mM NaCl, 50 mM Tris-HCl pH 7.2) is added per well for blocking. After 1 hr incubation at R.T., the wells are emptied, and 100 µl of sample (optionally diluted in dilution buffer (THT + 0.1% Casein)) is added. After another incubation at 1 hr at room temperature, the wells are washed 4 times with THT buffer, and 100 µl of a biotin-labelled antibody directed against the EGF-like domain (1 µg/ml) is added. After another 1 hr incubation at R.T., followed by 4 more washes with THT buffer, 100 µl of streptavidin-horse radish peroxidase (DAKO A/S, Glustrup Denmark, diluted 1/10000) is added. After another 1 hr incubation at R.T., followed by 4 more washes with THT buffer, 100 µl of TMB (3,3',5,5'-tetramethylbenzidine, Kem-enTech A/S, Denmark) is added. After 30 min incubation at

R.T. in the dark, 100 µl of 1 M H_2SO_4 is added and OD_{450nm} is determined. A standard curve is prepared using rhFVIIa (NOVOSEVEN®) ~~(NovoSeven®)~~.

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9) The table beginning at page 44, line 8 should be replaced with the following replacement table:

With markings:

Table 1.

Variant	Clotting time (Whole Blood Assay) $T_{variant}/T_{wt}$
rhFVIIa (reference)	1
D196K	0.4
D196N	0.4
K341Q	0.4
G237L	0.3
G237GAA	0.3

~~Table 1~~

Without markings:

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Variant	Clotting time (Whole Blood Assay) $T_{variant}/t_{wt}$
rhFVIIa (reference)	1
D196K	0.4
D196N	0.4
K341Q	0.4
G237L	0.3
G237GAA	0.3

10) The paragraph beginning at page 15, line 22 should be replaced with the following replacement paragraph:

With markings:

In still another embodiment of the invention the modification in position 237 is an insertion. In an interesting embodiment the insertion is selected from the group consisting of G237GXX, G237GXXX and G237GXXXX, wherein X is any amino acid residue. Preferably, X is selected from the group consisting of Ala, Val, Leu, Ile, Gly, Ser, Thr, in particular Ala. Specific examples of preferred insertions include G237GAA, G237GAAA (GAAA, SEQ ID NO:20) and G237GAAAA (GAAAA, SEQ ID NO:21). Most preferably, the insertions are G237GAA.

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